Applications for Pre-Market Review of Tobacco Products (PMTA) Webinar

November 1, 2011

Office of Small Business Assistance
Center for Tobacco Products

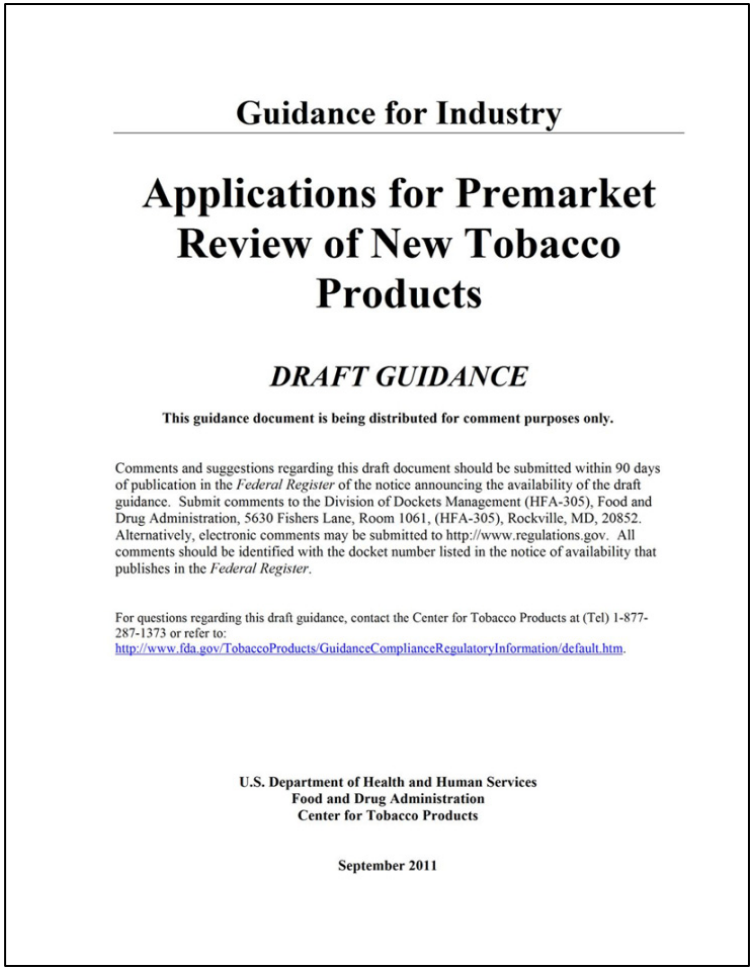
Introduction

PMTA Draft Guidance Webinar

Section 1

PMTA Draft Guidance Introduction

Draft Guidance Issued



Guidance for Industry

Applications for Premarket Review of New Tobacco Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-287-1373 or refer to:
http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

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Tobacco Product – section 201(rr)(1)

"…any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)."

New Tobacco Product – section 910(a)(1)

"(A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (B) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007."

Who Submits a PMTA?

- Persons seeking a marketing authorization order under section 910(c)(1)(A)(i) of the FD&C Act
- The draft guidance proposes a policy of limiting its enforcement of the requirements of section 910 to finished, regulated tobacco products.

When Should You Submit a PMTA?

You must submit a PMTA prior to the introduction or delivery for introduction of your new tobacco product into interstate commerce (unless you have obtained a substantial equivalence order or exemption under section 905(j))

PMTA and Substantial Equivalence (905(j))

If your new tobacco product . . .	*Then . . .*
Was marketed before March 22, 2011 and you submitted a 905(j) report for the product by March 22, 2011	***You may market your product unless and until FDA issues an order stating that the product is not substantially equivalent or not in compliance with the FD&C Act.***
Was marketed before March 22, 2011 and you did not submit a 905(j) report for the product by March 22, 2011	***You must cease marketing the product as of March 22, 2011 and cannot market the product again without first obtaining a marketing authorization order from FDA.***
Was first or will be first marketed on or after March 22, 2011	***You may not market the product without first obtaining a marketing authorization order from FDA.***

PMTA and Listing of Ingredients

- Sections 904(c)(1), (2), and (3) of the FD&C Act require manufacturers to submit information regarding the ingredients and additives of their tobacco products under specific timeframes.
- In the draft guidance, FDA proposes that you submit the information required under sections 904(c)(1), (2), or (3) prior to, or concurrent with, your PMTA and that you reference those submissions in your PMTA.

How will we Review a PMTA?

- Within 180 days
- Referral to the Tobacco Products Scientific Advisory Committee
- Withdrawal

Section 2

Contents of a PMTA

Statutory Requirements, FDA's Proposed Interpretation & Recommendations

A. Health Risk Investigations

910(b)(1). An application shall contain:

"full reports of all information. . . concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products"

A. Health Risk Investigations

Draft guidance: Full reports of all information…

- supportive, non-supportive, or adverse
- both clinical and non-clinical
- assessing…
  - » Constituents
  - » Toxicology
  - » Consumer exposure and use profiles
  - » Novel components
- both within and outside the U.S

A. Health Risk Investigations

Draft guidance: literature review…

- Provide an explanation of the scope of the literature review you conducted to discover relevant published studies
- Provide a bibliography of all published studies
- For each published study, include an abstract

A. Health Risk Investigations

Draft guidance: *For each study you submit include…*

- a summary of the results
- reasonably obtainable documentation

A. Health Risk Investigations

- ***Draft guidance:*** *a summary of the results*
  - Description of the study's objective
  - Description of the study's design
  - Description of any statistical analysis plan
  - Brief description of the findings and conclusions

A. Health Risk Investigations

- ***Draft guidance: reasonably obtainable documentation***
  - All actions taken to ensure reliability and protection of human subjects
  - Original study protocols
  - Investigator instructions
  - Statistical analysis plan
  - All raw data
  - All versions of questionnaires
  - All versions of case report forms
  - All informed consent forms
  - Full report of the findings

B. Components, Ingredients, Additives, Properties, and Operation

910(b)(1)(B). An application shall contain:

"a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product"

B. Components, Ingredients, Additives, Properties, and Operation

Draft Guidance:

1. Complete list of components, ingredients, and additives
2. Full narrative description of the product's features
3. Full narrative description of how consumers will use and operate the product

B. *Components, Ingredients, Additives, Properties, and Operation*

1. Draft guidance: Complete list of uniquely identified components, ingredients, and additives…

- …by quantity
- …with applicable specifications of each
- …with a description of the intended function of each

B. Components, Ingredients, Additives, Properties, and Operation

2. Draft guidance: Full narrative description of the product's properties including…

- …form, dimensions, construction…
- …design features….
- …tobacco blending, reconstitution, or manipulation…
- …performance criteria…
- …differences from similar products…
- …established shelf life.

B. Components, Ingredients, Additives, Properties, and Operation

3. Draft guidance: Full narrative description of the principle or principles of operation including…

- …how a consumer will use the product…
- …how a consumer will operate the product…
- …how long it takes to consume a single unit…
- …how the product's heat source functions.

C. Manufacturing and Processing

910(b)(1)(C). An application shall contain:

"a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, where relevant, packing and installation of the new tobacco product."

C. Manufacturing and Processing

Draft guidance:

A listing of all…

- …manufacturing, packing, and control sites

A narrative description, list, and summary of all…

- …standard operating procedures (SOPs)

Examples of relevant forms and records…

- …for the categories of information listed in the draft guidance.

C. Manufacturing and Processing

Draft guidance: Examples of relevant forms and records you can include…

- Manufacturing and production activities
- Personnel oversight and training
- Processes and controls for design and changes
- Supplier activities
- Validation and verification activities
- Pre-release testing procedures
- Complaints, nonconformance
- Corrective and preventative actions

D. Compliance with Standards

910(b)(1)(D). Identify any tobacco product standard under section 907 of the FD&C Act that would be applicable to your new tobacco product, and provide adequate information that either shows that your new tobacco product fully meets the tobacco product standard or justifies any deviation from that standard

E. Samples and Components

910(b)(1)(E). An application shall contain:

"samples of [your] tobacco product and of components thereof as the Secretary may reasonably require"

E. Samples and Components

Draft guidance: Provide samples…

- *… of both finished product and components*
- *…and a sufficient number of both*

Draft guidance: Provide summaries…

- *…of the results of any tests you performed on the lots(s) represented by the submitted samples.*

E. Samples and Components

Draft guidance: a sufficient number…

Cigarette and cigarette-like tobacco products	*4,000 pieces (~20 cartons)*
Roll-your-own tobacco products	*4,000 grams*
Smokeless tobacco in pre-measured units of use	*200 pieces*
Loose smokeless tobacco	*200 grams*
Finished component tobacco products sold separately to consumers	*200 pieces*

F. Proposed Labeling

910(b)(1)(F). Include specimens of all proposed labeling for your new tobacco product

F. Proposed Labeling

Labeling is defined in section 201(m) of the FD&C Act as, “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article,” and includes labels, inserts/onserts, instructions, and other accompanying information or materials.

Section 3

Appropriate for the Protection of the Public Health

Basis For Determination

Protection of the Public Health

910(c)(2)(A). FDA is required to deny applications where "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health"

Protection of the Public Health

FD&C Act: The determination's basis…

- …the risks and benefits to the population as a whole including…
  - …both user and nonusers
  - …the likelihood existing users will stop
  - …the likelihood non-users will start
- …well-controlled investigations, when appropriate

Protection of the Public Health

Draft guidance: Well-Controlled Investigations

A. Product chemistry

B. Nonclinical studies

C. Studies in adult human subjects

A. Well-Controlled Investigations

A sampling of questions listed in the draft guidance…

- How do the health risks
  - …of your product compare to the health risks of other products on the market?
  - …of switching from another product to your product compare to the health risks associated with quitting?
- How will your new tobacco product…
  - …affect the likelihood that never-users and former-users will use your new product?
  - …affect the likelihood that current users will cease using tobacco products?

A. Well-Controlled Investigations

Draft guidance: Your scientific evaluations should…

- …use control groups of comparator products
- …assess various tobacco use levels
- …include biomarkers where appropriate
- …follow a pre-specified statistical analysis plan

B. Product Chemistry Data

Draft guidance suggests that you

Report the levels of harmful and potentially harmful constituents…

- …including smoke constituents…
  - Using both ISO and Canadian Intense smoking regimens
- …in a tabular format described in the draft guidance.

and that you provide documentation of accreditation by a nationally or internationally recognized external accreditation organization.

B. Product Chemistry Data

Draft guidance: …tabular format…

Use separate columns, in the order listed below (from left to right) for each of the following:

- Constituent name
- Constituent's common name(s)
- Corresponding Chemical Abstract Services number
- Unit of measure
- Level measured for the submitted product
- Sample size
- Method of measuring and
- References

C. Nonclinical Studies

Draft guidance: Your nonclinical investigations should…

…evaluate

- …toxicity, abuse liability, and carcinogenicity

…generate

- …data to evaluate these properties using some combination of in vitro, in vivo, and/or ex vivo studies

C. Nonclinical Studies

Draft guidance:

Your study designs should…

- …include adequate sample sizes

Your study models should…

- …be sufficiently sensitive to endpoints
  - Provide evidence and an explanation of the sensitivity and probative value of the model

Review the sample explanation in the draft guidance.

D. Studies in Adult Human Subjects

Draft guidance: Assess the effects of the new tobacco product on human health and behavior:

- pattern of use and tobacco use topography
- toxicant exposure and biological effect
- abuse potential
- and consumer perception

D. Studies in Adult Human Subjects

Draft guidance: Your study protocols should…

- …specify the study design, conduct, and statistical analysis plan
- …interpret statistical measures of uncertainty
  - consider the potential contribution of bias to the p-value, confidence interval, or other inferences.

D. Studies in Adult Human Subjects

Draft guidance: Your studies should be generalizable to the population of the U.S., by considering…

- …study size
  - consider oversampling populations likely to be affected by introduction of the product
- … subject selection
  - reflective of the diversity of the adult user population
  - control group based on endpoints
- …study duration
  - based on endpoints to be evaluated

D. Studies in Adult Human Subjects

Draft guidance: Your studies should evaluate…

- …user exposure to tobacco-related compounds
- …user health risk and disease incidence
- …product use patterns
- …abuse liability and addictiveness
- …cessation rates for users
- …consumer perceptions
  - » **Including risk perceptions based on the product itself, as well as on the packaging and labeling of the new tobacco product**

Section 4

Investigational Use of New Tobacco Products

A. Investigational Use

Draft guidance: FDA plans to issue regulations pursuant to section 910(g) providing conditions under which tobacco products may be exempted from the requirements of section 910 when used for investigational purposes.

A. Investigational Use

Until these regulations are issued, the draft guidance proposes a policy in which FDA will consider exercising discretion, on a case-by-case basis, in enforcing the premarket review requirements of Chapter IX of the FD&C Act, in some circumstances, for the purposes of investigational use of new tobacco products.

A. Exemption for Investigational Use

Draft guidance: Examples of specifications for all studies to ensure studies are well-controlled, data are reliable, and subjects are adequately protected…

- …limit distribution of the investigational product
- …do not promote or test market investigational product for commercial distribution
- …account for receipt, use, and disposition of investigational product
- …label the product "for investigational use only"

A. Exemption for Investigational Use

Draft guidance: Investigators of:

- ***Clinical studies…***
  - …take measures to ensure the rights, safety, and welfare of human subjects have been protected
  - …all study subjects are current users at least 21 years of age
- ***Nonclinical studies…***
  - …follow good laboratory practices

B. Study Design Meeting

Draft guidance: Applicants who would like to study their new tobacco products should contact the Office of Science at the Center for Tobacco Products to discuss submission of a study protocol and/or study endpoints for investigations intended to support a PMTA

B. Study Design Meeting

Process proposed in draft guidance:

1. Meeting Request
2. Scheduling
3. Meeting Package

B. Study Design Meeting

Draft guidance: Meeting request should include…

- …adequate information to assess utility and the purpose of the meeting
- …a description of the product
- …the role of your planned study in overall product development plans
- …specific questions
- …a proposed agenda
- …a list of expected attendees
- …an investigational plan
  - Including a **summary of your proposed study protocol(s)**.

B. Study Design Meeting

Draft guidance:…summary of study protocol(s) should include…

- ...study objectives
- …study hypothesis or hypotheses
- …background information
- …study design
- …study population
- …human subject protection information
- …primary and secondary endpoints
- …statistical analysis plan
- …data collection procedures
- …duration of baseline and follow-up assessments

B. Study Design Meeting

Draft guidance: After FDA schedules a meeting, you should submit a fully paginated meeting package containing…

- …a detailed description of the product
- …status of product development
- …investigational plan
- …specific questions to be discussed
- …background information relevant to those questions

C. Studies Outside the U.S.

The draft guidance proposes that studies conducted outside the U.S. should employ particular practices to…

- …ensure that the rights, safety, and welfare of human subjects have been protected
- …conform with applicable standards or laws for good clinical practice